

Commentary

# Risk Assessment for Acid Aerosols

by Roy E. Albert\*

My experience has involved a great deal of methodology development for carcinogen risk assessment in the Environmental Protection Agency, but none for acid aerosols. However, there are some insights from carcinogen risk assessment that do apply to acid aerosols. The greatest need is to understand mechanisms of action as the basis for characterizing dose response relationships at low levels of exposure.

Risk assessment is an orderly assembly of the evidence with some agreed upon guidelines as to how to make judgments about the nature (qualitative assessment) and magnitude (quantitative assessment) of health hazards. Risk assessment provides guidance for regulation, but the impetus for regulation comes from public pressure to remedy perceived health problems. Risk assessment answers the question, What is the problem? Risk management deals with the question of, What are we going to do about it? Risk assessment can be likened to describing to regulators the picture on a jigsaw puzzle where many of the pieces are missing. Plausible assumptions are used to fill in the gaps. The larger the range of uncertainty, the more room for personal or institutional bias. Individuals who have very different institutional loyalties and pressures can produce very different risk assessments for the same material where large uncertainties exist. Risk assessments for formaldehyde, as a carcinogen, is a case in point: whether formaldehyde is described as extremely hazardous or entirely safe depends on who does the assessment.

Carcinogen risk assessment, both in terms of its guidelines and also in terms of the assessment of specific agents, has been an area of extreme contention. The alternative to risk assessment is standard setting by the use of the highest no-observable-effect level (NOEL) with arbitrary safety factors. This has been described as "Stone Age" toxicology, and, in my opinion, has been a blight on the development of toxicology as a science. For all its contentiousness, risk assessment has had the beneficial result of forcing a clear distinction between what is known and what is not known and laying bare the assumptions that are necessary to the development of exposure standards. There is no meaningful risk assessment without quantitation of

the associated hazards. There is no quantitation without dose-response relationships. Because of the uncertainties in observable low level effects, there can be confidence in the dose-response relationships only with an understanding of mechanisms of action.

There are some sharp contrasts between carcinogens and acid aerosols in terms of risk assessment and management. In terms of the impetus to regulate, there was overwhelming pressure beginning in the 1970s for the control of environmental carcinogens. The lack of progress in cancer treatment led to the National Program for the Conquest of Cancer beginning in 1970. There was an explosive growth of the numbers of chemicals that were being introduced by the chemical industry into the environment, and increasing numbers of chemicals were shown to be carcinogenic in animal and epidemiological studies. Epidemiologic evidence strongly supported a dominant role of environmental factors in the causation of cancer. So there was initially a very large impetus for the regulation of carcinogens and, hence, the assessment of suspect carcinogens. In the case of acid aerosols, there is a smaller impetus for regulation because acid aerosols are in part regulated under the control of atmospheric particulates.

The regulatory objective for carcinogens is to diminish the tremendous load of cancer mortality as the second leading cause of death. In the case of acid aerosols, the regulatory objective is less pressing: to eliminate mortality among the moribund from heart and pulmonary disease and the prevention of acute impairments of pulmonary function and acute respiratory infections.

The regulatory strategy for carcinogens is involved because of different Congressional laws at different times. It ranges from the banning of carcinogenic additives under the Delaney clause of the Food and Drug Act; the use of a zero concentration as a target under the Drinking Water Act; weighing risks and benefits under the Federal Insecticide, Rodenticide and Fungicide Act and the Toxic Substances Control Act; and specifying excess cancer risk levels of  $10^{-5}$  to  $10^{-7}$  for lifetime exposure as a guide for state regulation of carcinogenic water pollutants. The Clean Air Act, in regard to acid aerosols, calls for zero risk with a margin of safety, although the EPA has made strenuous efforts to ease this requirement.

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The dominant dose-response model used for carcinogen risk assessment is linear nonthreshold. By contrast, it is generally assumed that there is a threshold for acid aerosol effects, but the shape of the dose-response curve is not established. In both cases, understanding of mechanisms that would provide the basis for low dose-response modeling is limited; in both cases, individual susceptibility is an important factor in determining response to low levels of exposure. The nature of the response is different with carcinogens than acid aerosols. In the case of carcinogens, the response is quantal. With decreasing dose, there is no change in the severity (i.e., malignancy) of induced tumors, but simply a reduction in the frequency. In the case of acid aerosols, as is characteristic of most toxicants, a decrease in dose results both in a decrease in the severity of the response and in the proportion of individuals showing responses; the effect fades away.

In the case of carcinogens, risk assessment is mostly done on individual compounds or, in some cases, on mixtures which result from single sources, for example, diesel emissions. In the case of acid aerosols, the situation is more complex because the effects of acid aerosols appear to be modified by a variety of other associated air pollutants. Hence, the biggest differences between risk assessment for carcinogens and acid aerosols is the immense drive for regulation resulting in the acceptance of an extremely conservative non-threshold dose-response model for carcinogens in contrast to a weaker drive for regulation with a threshold dose-response pattern for acid aerosols.

The rest of my comments deal with the risk assessment needs for acid aerosols. The first need is to get a better definition of the end points of response to acid aerosols. Mortality as an end point is straightforward, as is the induction of an increased incidence of respiratory disease although the severity of the latter effect at different levels might be an aspect that could be looked at. Another aspect that needs clarification is the meaning, in terms of pulmonary performance, of small decrements in pulmonary function test results as, for example, when children show a small decrement in a FEV<sub>1</sub> evaluation during a summer haze episode. The most important area of uncertain end points is the chronic effects of acid aerosols. What is the nature of the structure and functional effects of long-term exposures to acid aerosols, particularly in relationship to the decrements of pulmonary function associated with aging? Does acid aerosol exposure have a amplifying effect on the carcinogenic action of other air pollutants as has been demonstrated with sulfur dioxide in the rat lung with concurrent exposure to benzopyrene? And, if so, what is the nature of the dose-response relationship for such an effect?

As indicated earlier, dose-response relationships are critical issues in quantitative risk assessment. Human studies are useful in identifying the nature of the effects and in providing limited information on dose response. Animals generally provide a better definition

of dose-response but always with the uncertainty as to the applicability for humans. The combination of human, animal, cellular, and subcellular responses provides information on dose-response mechanisms that give an indication of the shape of the dose response. When the shape is combined with benchmark responses in humans one can get a reasonable quantitative model for risk assessment. The dearth of mechanistic knowledge has been the bane of carcinogen risk assessment. Holma's work reported that this meeting, on the role of mucus in protecting against acid aerosols, is a good start on obtaining a theoretical understanding of dose-response mechanisms. But there are a lot of unanswered questions, such as, What is the thickness and rate of production of mucus at various levels of the tracheobronchial tree? Is mucus distributed uniformly over the surface of the tracheobronchial mucosa in normal subjects? This is not the case in individuals chronically exposed to cigarette smoke and air pollutants who have patches bare of mucus in regions of squamous metaplasia. This is a problem very similar to that for formaldehyde where the issue is whether, at low concentrations, the penetration through the mucous layer is zero. Can a similar sort of analysis be extended to defense mechanisms against acid particulates in the alveoli? Here, there is no mucus. Does the liquid film on the surface of the alveoli have buffering capacity, and if so, how much? Is there a cellular exudate at the site of the acid particle deposition which neutralizes the acidity? Does the acid coating facilitate the penetration of such particles into the interior of cells which then get neutralized? There is some analogy here with the so-called hot particle problem in the field of ionizing radiation, where the problem is the nature and magnitude of the toxicologic effects of isolated radioactive particles that are deposited in the lung both in terms of chronic damage and cancer induction.

A better understanding of the mechanism of the other end points for the effects of acid aerosols discussed above such as increased mortality, acute bronchitis, exacerbation of chronic obstructive pulmonary disease, and decreased pulmonary function would significantly contribute to a better definition of dose-response relationships to be used in quantitative risk assessment.

A particular difficulty with the characterization of dose-response for acid aerosols is that they do not exist in isolation in the atmosphere, and, more importantly, their effects are synergistic with other pollutants, especially ozone. This raises mechanistic questions as to the bases for the interactions and the need to define dose-response relationships for acid aerosols in the presence of other atmospheric pollutants.

In summary, the most important needs for the risk assessment of acid aerosols is a better definition of end points, particularly chronic effects, and a better understanding of mechanisms of action as they throw light on the nature of the dose-response relationships at low levels of exposure.